Targeted Type 2 Alveolar Cell Depletion. A Dynamic Functional Model for Lung Injury Repair.

Journal: Am J Respir Cell Mol Biol

Publication Year: 2016

Authors: Orquidea Garcia, Michael J Hiatt, Amber Lundin, Jooeun Lee, Raghava Reddy, Sonia Navarro, Alex Kikuchi, Barbara Driscoll

PubMed link: 26203800

Funding Grants: Bridges to Stem Cell Research at Pasadena City College

Public Summary:
Type 2 alveolar epithelial cells (AEC2) are regarded as the progenitor population of the alveolus responsible for injury repair and homeostatic maintenance. Depletion of this population is hypothesized to underlie various lung pathologies. Current models of lung injury rely on either uncontrolled, nonspecific destruction of alveolar epithelia or on targeted, nontitratable levels of fixed AEC2 ablation. We hypothesized that discrete levels of AEC2 ablation would trigger stereotypical and informative patterns of repair. To this end, we created a transgenic mouse model in which the surfactant protein-C promoter drives expression of a mutant SR39TK herpes simplex virus-1 thymidine kinase specifically in AEC2. Because of the sensitivity of SR39TK, low doses of ganciclovir can be administered to these animals to induce dose-dependent AEC2 depletion ranging from mild (50%) to lethal (82%) levels. We demonstrate that specific levels of AEC2 depletion cause altered expression patterns of apoptosis and repair proteins in surviving AEC2 as well as distinct changes in distal lung morphology, pulmonary function, collagen deposition, and expression of remodeling proteins in whole lung that persist for up to 60 days. We believe SPCTK mice demonstrate the utility of cell-specific expression of the SR39TK transgene for exerting fine control of target cell depletion. Our data demonstrate, for the first time, that specific levels of type 2 alveolar epithelial cell depletion produce characteristic injury repair outcomes. Most importantly, use of these mice will contribute to a better understanding of the role of AEC2 in the initiation of, and response to, lung injury.

Scientific Abstract:
Type 2 alveolar epithelial cells (AEC2) are regarded as the progenitor population of the alveolus responsible for injury repair and homeostatic maintenance. Depletion of this population is hypothesized to underlie various lung pathologies. Current models of lung injury rely on either uncontrolled, nonspecific destruction of alveolar epithelia or on targeted, nontitratable levels of fixed AEC2 ablation. We hypothesized that discrete levels of AEC2 ablation would trigger stereotypical and informative patterns of repair. To this end, we created a transgenic mouse model in which the surfactant protein-C promoter drives expression of a mutant SR39TK herpes simplex virus-1 thymidine kinase specifically in AEC2. Because of the sensitivity of SR39TK, low doses of ganciclovir can be administered to these animals to induce dose-dependent AEC2 depletion ranging from mild (50%) to lethal (82%) levels. We demonstrate that specific levels of AEC2 depletion cause altered expression patterns of apoptosis and repair proteins in surviving AEC2 as well as distinct changes in distal lung morphology, pulmonary function, collagen deposition, and expression of remodeling proteins in whole lung that persist for up to 60 days. We believe SPCTK mice demonstrate the utility of cell-specific expression of the SR39TK transgene for exerting fine control of target cell depletion. Our data demonstrate, for the first time, that specific levels of type 2 alveolar epithelial cell depletion produce characteristic injury repair outcomes. Most importantly, use of these mice will contribute to a better understanding of the role of AEC2 in the initiation of, and response to, lung injury.